Int J Clin Exp Med 2019;12(1):1226-1233
www.ijcem.com /ISSN:1940-5901/IJCEM0078809

Original Article

Randomized comparison of sevoflurane versus propofol on organ blood flow after partial thoracic aortic cross-clamping

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Received May 1, 2018; Accepted July 26, 2018; Epub January 15, 2019; Published January 30, 2019

Abstract: Clamping of the aorta leads to an ischemia-reperfusion syndrome, hemodynamic consequences, and changes on serum markers of cellular injury such as pro-/anti-inflammatory cytokines and oxygen free radicals. Sevoflurane and propofol are commonly used during cardiovascular surgery. Sevoflurane induces organ protection in ischemia-reperfusion syndrome and has showed potential to be superior to propofol in ischemia induced by total occlusion of the thoracic aorta (sevoflurane shows better hemodynamic stability and lower release of markers of tissue injury), however this effect in partial cross-clamping has not been investigated. The aim of this study was to assess the effect of sevoflurane and propofol on organ blood flow after partial thoracic aortic cross-clamping. Ten healthy mini-pigs were divided into 2 groups (5 per group) according to the anesthetic received (sevoflurane or propofol). After median sternotomy, a partial cross-clamp was applied on the ascending thoracic aorta during 20 min. Organ blood flow (measured by colored microspheres), serum markers of tissue injury, markers of inflammation and nitric oxide were assessed at baseline (before partial aortic cross-clamping) and 30 minutes after removal of partial aortic cross-clamping. No significant differences were recorded between the groups on blood flow in the brain, heart, liver, lung, kidney, or ileum after 30 minutes reperfusion. The markers of tissue injury, markers of inflammation and nitric oxide were similar in both groups. In summary, the results of our study provide that sevoflurane is not superior to propofol in relation to blood flow, markers of tissue injury, markers of inflammation and nitric oxide after partial cross-clamping of the thoracic aorta.

Keywords: Partial thoracic aortic cross-clamping, propofol, sevoflurane, blood flow

Introduction

Cardiovascular surgery has a high mortality rate. Aortic clamping elicits an ischemia-reperfusion syndrome that affects all organs, causing dysfunction and multi-organ failure [1]. Apart from changes on organ blood perfusion, clamping of the aorta leads to hemodynamic consequences, changes on serum markers of cellular injury and pro- and anti-inflammatory cytokine release, and oxygen free radical production [2-4].

Sevoflurane and propofol are commonly used on cardiovascular surgery. Several studies have reported changes in organ blood flow in response to their administration [5-11], however this effect has not been analyzed on partial thoracic aortic cross-clamping. Sevoflurane induces organ protection in ischemia-reperfusion syndrome and this protection is due to pharmacologic pre-conditioning and post-conditioning [12, 13]. Sevoflurane showed potential to be superior to propofol in ischemia induced by total occlusion of the thoracic aorta (sevoflurane shows better hemodynamic stability and lower release of markers of tissue injury) [14], however this effect in partial cross-clamping has not been investigated.

This study has been performed on the hypothesis that sevoflurane-based anesthesia would

Table 1. Markers of tissue injury and NO in both groups at baseline and after removal of PAC

	PROPOFOL n = 5	SEVOFLURANE n = 5	*P* Values
ALT (U/L)			
Baseline	33 ± 2	26 ± 1	0.054
After PAC	29 ± 2	25 ± 2	0.221
AST (U/L)			
Baseline	35 ± 3	32 ± 5	0.667
After PAC	50 ± 10	35 ± 3	0.116
Bilirubin (mg(dL)			
Baseline	0.32 ± 0.10	0.18 ± 0.05	0.273
After PAC	0.25 ± 0.06	0.13 ± 0.02	0.081
GGT (U/L)			
Baseline	50 ± 6	43 ± 5	0.398
After PAC	63 ± 12	55 ± 8	0.584
AP (U/L)			
Baseline	95 ± 7	76 ± 6	0.073
After PAC	82 ± 8	72 ± 8	0.428
LDH (U/L)			
Baseline	395 ± 43	401 ± 41	0.915
After PAC	330 ± 19	331 ± 13	0.943
Creatinine (mg/dL)			
Baseline	0.51 ± 0.02	0.59 ± 0.03	0.059
After PAC	0.44 ± 0.03	0.57 ± 0.06	0.085
Lactic Acid (mmol/L)			
Baseline	1.1 ± 0.1	1 ± 0.1	0.550
After PAC	1.5 ± 0.5	1.1 ± 0.2	0.453

Data are expressed as the mean ± standard error of the mean. ALT: alanine transaminase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transpeptidase; AP: alkaline phosphatase; LDH: lactate dehydrogenase.

increase organs blood flow compared to propofol-based anesthesia after partial aortic cross-clamping. The primary objective was to study which anesthetic regime (sevoflurane or propofol) is superior on organ blood flow (brain, heart, lung, liver, kidney, and ileum) after partial thoracic aortic cross-clamping. Our secondary objective was to evaluate the effect of sevoflurane and propofol on serum markers of cellular injury, inflammation and nitric oxide (NO).

Material and methods

Animals

The line of pigs used in the study was created by Dr. Sachs at the National Institutes of Health (Bethesda, Maryland, USA). The animals used in our experiment were from the farm of the Technological Institute of Agrarian Development (EX 013-C) (Community of Madrid, Spain). The pigs were moved from this farm to the Experimental Medicine and Surgery Unit, Gregorio Marañón University General Hospital (ES280790000087), where they remained under a controlled environment until the intervention (20-22°C and relative humidity of 55%). The study was performed in accordance with European Union guidelines on the protection of animals used for experimental and other scientific purposes (Directive 2010/63/EU and Spanish Royal Decree RD 53/2013 BOE) and was approved by the Ethics Committee, Gregorio Marañón University General Hospital, Madrid, Spain.

Experimental design

The study was conducted with ten healthy mini-pigs. Animals were block-randomized (Microsoft Excel 2003) to receive either propofol in continuous perfusion as anesthetic maintenance (propofol group, n = 5) or sevoflurane (sevoflurane group, n = 5). Two specific moments of the study were analyzed: before the partial aortic cross-clamp (baseline) and 30 minutes after removal of the partial aortic cross-clamp.

Anesthesia and surgical protocol

The animals were simultaneously premedicated with intramuscular ketamine 20 mg/kg (Ketolar, Parke-Davis, Madrid, Spain) and atropine 0.04 mg/kg (Atropina Braun, Serra-Pamies, Reus, Spain). The pigs were provided with oxygen 100% via a facemask, a 20 G cannula was inserted into an ear vein, and anesthesia was induced with intravenous fentanyl 2.5 μg/kg (Fentanest, Kern Pharma, Barcelona, Spain) and propofol 4 mg/kg (Diprivan 1%, AstraZeneca, Madrid, Spain). After intubation, each animal was connected to a volume-controlled ventilator (Dräger SA1, Dräger Medical AG, Lübeck, Germany) with FIO_2 of 1, an inspiratory: expiratory ratio of 1:2, a tidal volume of 12-15 mL/kg, and the respiratory rate adjusted to maintain normocapnia as previously described [15]. Anesthesia was maintained for all animals with intravenous fentanyl (2.5 μg/kg/30 minutes) and either propofol in continuous infusion (11-12 mg/kg/h) for

Table 2. Inflammatory and oxidative stress response in both groups at baseline and after removal of PAC

	PROPOFOL n = 5	SEVOFLURANE n = 5	*P* Values
Hsp70 (ng/ml)			
Baseline	5.12 ± 1.11	4.08 ± 0.27	0.386
After PAC	5.68 ± 1.49	4.55 ± 0.48	0.489
C3a (ng/ml)			
Baseline	22.35 ± 4.75	13.11 ± 4.10	0.191
After PAC	18.92 ± 3.29	13.26 ± 3.77	0.301
NO (μM)			
Baseline	610.06 ± 33.96	732.61 ± 129.93	0.514
After PAC	418.12 ± 66.44	691.27 ± 11.81	0.143
TNF-α (pg/ml)			
Baseline	42.70 ± 8.24	33.56 ± 16.70	0.615
After PAC	29.16 ± 0.92	34.68 ± 10.68	0.566

Data are expressed as the mean ± standard error of the mean. Hsp70: heat shock protein 70; C3a: complement 3 activated; NO: nitric oxide; TNF-α: tumor necrosis factor.

the propofol group or 2% sevoflurane for the sevoflurane group as previously described [11]. All animals received an infusion of saline solution (8 mL/kg/h). After median sternotomy, a partial cross-clamp was applied on the ascending thoracic aorta during 20 minutes.

Markers of tissue injury

Serum levels of total bilirubin, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transpeptidase, and alkaline phosphatase were evaluated as parameters of hepatobiliary function. Creatinine and urea were studied as parameters of renal function. Lactate dehydrogenase and lactate were measured as non-specific indicators of tissue injury. All previously described markers of tissue injury were studied before the partial aortic cross-clamp was applied (baseline) and 30 minutes after the partial aortic cross-clamp was removed.

Markers of inflammatory response and nitric oxide

HSPA1A was quantified (Hsp72/Hsp70) [16] in plasma samples through ELISA kit EKS-715 (Assay-Designs-Stressgen, Ann Arbor, Michigan, USA). C3 was quantified in porcine plasma samples through the ELISA technique using the *Porcine Complement 3* (C3) ELISA kit (N° CSB-E06920p, Cusabio, Wuhan, Hubei Province 430223, P. R. China). TNF-α was quantified in plasma samples through the ELISA technique (Quantikine Porcine TNF-α, R&D Systems, Abingdon, UK). NO was quantified in plasma samples through the *Nitric Oxide Colorimetric Assay Kit* (Oxford Biomedical research, Oxford, MI 48371, USA).

All previously described markers were studied before the partial aortic cross-clamp was applied (baseline) and 30 minutes after the partial aortic cross-clamp was removed.

Organ blood flow measurements

Colored microspheres (Dye-Trak, Triton Technology Inc., San Diego, California, USA) were used to measure organ blood flow. Before the partial aortic cross-clamp was applied (baseline), yellow microspheres (diameter 12 microns) were injected into the left atrium (1.5 million microspheres per injection). Also, violet microspheres were injected 30 minutes after removal of the partial aortic cross-clamp.

After each experiment, the animal was sacrificed using potassium chloride. Tissue samples of both brain hemispheres (right and left frontal lobe), heart (right and left ventricles), liver, lung (middle lobe of right lung), kidney and ileum were obtained to measure organ blood flow. The microspheres were isolated from the tissue by digestion with potassium hydroxide and then were centrifuged. The dyes were extracted from the colored microspheres and, using spectrometry, the colors were separated and the concentration was measured [17, 18].

Data analysis and statistics

The primary endpoint was organ blood flow, which was compared between the two groups. The variables were expressed as mean ± SEM. We used the Kolmogorov-Smirnov test to analyze the distribution of quantitative variables; between-group comparisons were based on the t-test for independent samples. Statistical significance was set at a *P* value of <0.05. The statistical analysis was performed using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp, Armonk, NY, USA) and S-PLUS 6.1.

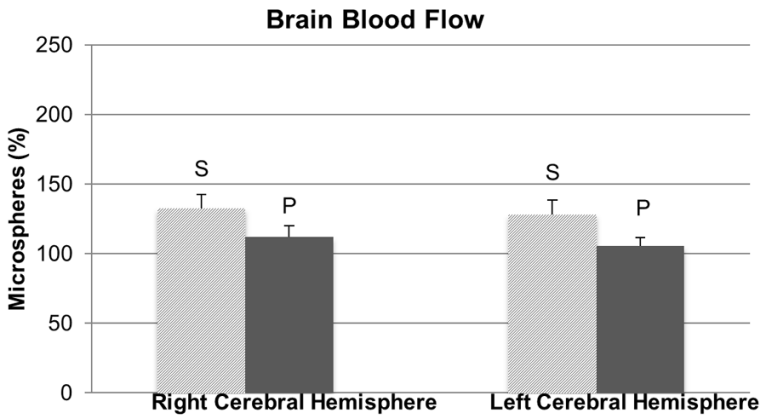

Figure 1. Brain blood flow. Data are expressed as the mean ± SEM. Cerebral blood flow in the right frontal lobe and left frontal lobe of pigs in both groups, sevoflurane (S) and propofol (P), after removal of partial aortic cross-clamping.

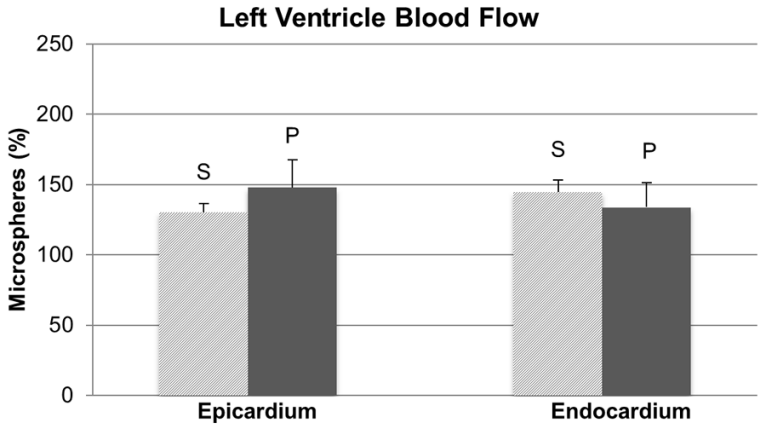

Figure 2. Left ventricle blood flow. Data are expressed as the mean ± SEM. Blood flow in the left ventricle of pigs with in both groups, sevoflurane (S) and propofol (P), after removal of partial aortic cross-clamping.

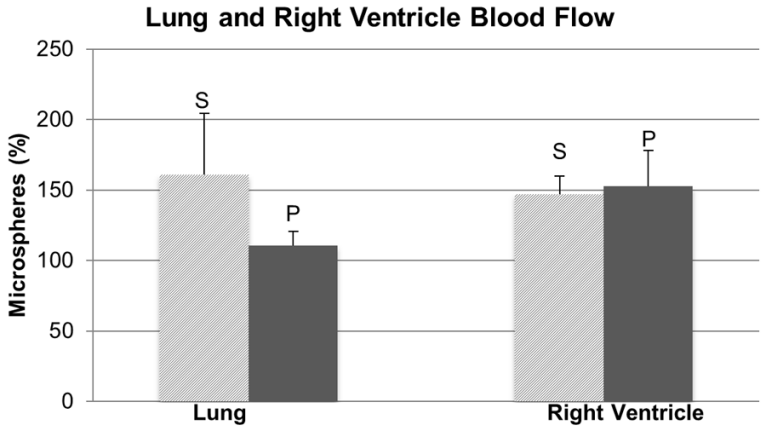

Figure 3. Lung and right ventricle blood flow. Data are expressed as the mean ± SEM. Blood flow in the lung and the right ventricle of pigs in both groups, sevoflurane (S) and propofol (P), after removal of partial aortic cross-clamping.

Results

Physiological parameters

There were not statistically significant differences between both groups (sevoflurane versus propofol) regarding age (143 ± 7 versus 126 ± 10 days, $P = 0.28$), weight (34 ± 1 versus 25 ± 3 kg, $P = 0.052$) and height (97 ± 2 versus 87 ± 1 cm, $P = 0.07$).

Effect of anesthetics on markers of tissue injury

Serum levels of markers of tissue injury were similar in both groups in both study moments (**Table 1**).

Effect of anesthetics on markers of inflammatory response and nitric oxide

There was not a statistically significant difference in the inflammatory response nor in NO levels between the sevoflurane and propofol groups at baseline and after removal of the partial aortic cross-clamp (PAC) (**Table 2**).

Effect of anesthetics on organ blood flow

Blood flow was similar in the brain (**Figure 1**), left ventricle heart (**Figure 2**), right ventricle (**Figure 3**), lung (**Figure 3**), kidney (**Figure 4**), liver (**Figure 5**) or ileum (**Figure 5**) between the sevoflurane and propofol groups in both moments reviewed (baseline and 30 minutes after removal of the partial aortic cross-clamp).

Discussion

The results of this study show that sevoflurane is not superior to propofol on organ blood flow, markers of tissue injury, markers of inflammation and

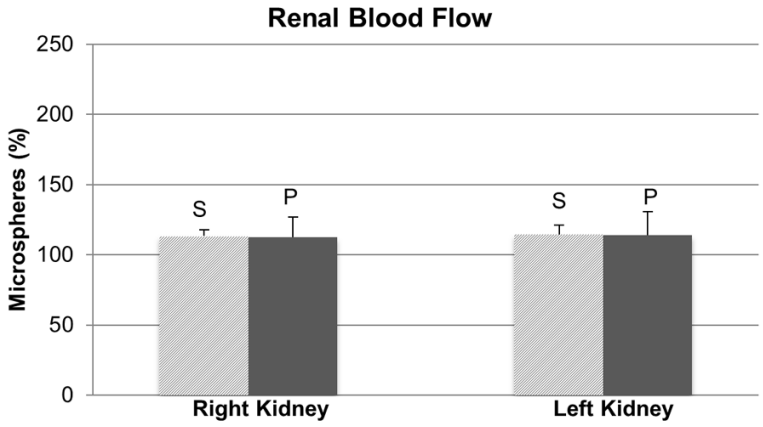

Figure 4. Renal blood flow. Data are expressed as the mean ± SEM. Blood flow in the kidney of pigs in both groups, sevoflurane (S) and propofol (P), after removal of partial aortic cross-clamping.

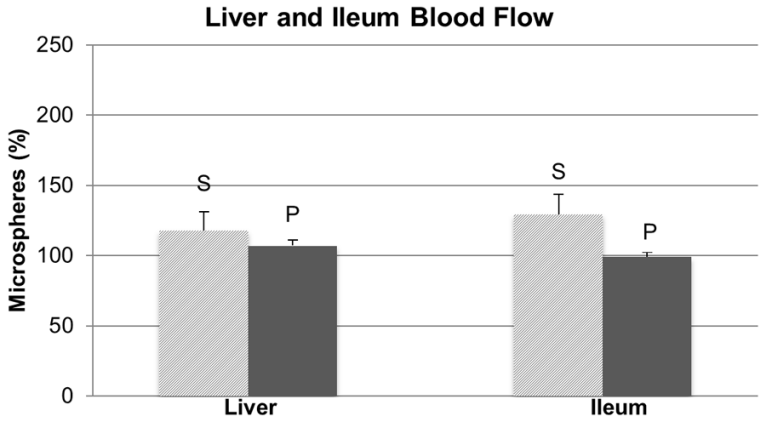

Figure 5. Liver and ileum blood flow. Data are expressed as the mean ± SEM. Blood flow in the liver and the ileum of pigs in both groups, sevoflurane (S) and propofol (P), after removal of partial aortic cross-clamping.

NO after partial cross-clamping of the thoracic aorta in pigs. To our knowledge, this is the first study that proves the similar effect of sevoflurane and propofol on reperfusion after partial thoracic aortic cross-clamping in a porcine model. If these results are confirmed in humans, anesthesiologists could use two anesthetic regimes (sevoflurane and propofol) in clinical settings with a partial cross clamp.

Because increased ascending aortic manipulation (aortic clamp) has been associated with postoperative complications, the focus has concentrated on innovating techniques (clamping strategies) to minimize manipulation of the thoracic aorta [19-23]. The partial thoracic aortic cross-clamping is used in human clinic during off-pump coronary artery bypass [20] and the implantation of left ventricular assist devices.

Ischemia-reperfusion injury (aortic cross-clamping) is a major problem in cardiovascular surgery. Reperfusion of ischemic tissues results in inflammatory response, microvascular dysfunction and multiple organ dysfunction syndrome [25]. Therefore patients who have undergoing cardiovascular surgery need special anesthetic management to limit or prevent ischemia-reperfusion injury.

Effect of anesthetics on ischemia-reperfusion

Sevoflurane and propofol are commonly used on cardiovascular surgery. Several studies have reported changes in organ blood flow in response to the administration of sevoflurane and propofol [5-11]. We have reported previously that sevoflurane increases blood flow in brain, liver, and heart tissue after implantation of left ventricular assist devices in a porcine model [11].

Sevoflurane induces pre-conditioning and attenuates myocardial ischemia/reperfusion injury via caveolin-3-dependent cyclooxygenase-2 inhibition, AMP-activated protein kinase, and anti-oxidative effects in experimental studies [26-28] and decreases transcript levels for platelet-endothelial cell adhesion molecule-I in human studies [13]. Despite cardioprotective effects of sevoflurane due to preconditioning properties and beneficial effects during reperfusion, in our study the organ blood flow, markers of tissue injury, markers of inflammation and NO after 30 minutes of reperfusion were similar in both groups, sevoflurane and propofol.

Annecke et al. [14] showed that sevoflurane compared to propofol attenuates the hemodynamic sequelae of reperfusion injury and the release of serum markers of cellular injury after

60 minutes of reperfusion following thoracic-aortic occlusion in pigs. In our study there were not differences on markers of tissue injury. This finding was consistent with similar organ blood flow in both groups on partial cross-clamping.

The inflammatory (TNF-α, C3a, Hsp70) response and the overproduction of reactive oxygen species play an important role in the pathophysiology of ischemia-reperfusion injury [25, 29, 30]. Sevoflurane, but not propofol, decreases inflammatory markers (TNF-α) after cross-clamping in patients undergoing coronary artery bypass graft surgery [29]. Our study showed no differences in this pro-inflammatory cytokine level.

Propofol attenuates ischemia-reperfusion injury due to the increase of nitric oxide (NO) synthase activity and NO production [31]. However, in our study we found no differences in NO between both groups, sevoflurane and propofol.

Benefit of the results for the clinics

The ischemia-reperfusion caused by aortic clamping is a problem in clinical practice in cardiovascular surgery. There are novel therapeutic strategies for limiting or preventing ischemia-reperfusion injury: during on-pump coronary artery bypass grafting, the use of a single cross-clamp compared with the double clamp technique decreased the risk of postoperative stroke [19]; minimally invasive left ventricular assist devices insertion technique using a partial cross-clamp [32]; and therapeutic approaches like ischemic preconditioning [25]. Sevoflurane induces organ protection in ischemia-reperfusion injury in humans by preconditioning [13], however our results showed that, after removal of partial aortic cross-clamping, there was no significant difference between both groups, sevoflurane, and propofol. Therefore, when choosing the anesthetic regime, several factors would have to be taken into account: the alteration of plasma propofol concentrations during cardiopulmonary bypass (CPB), due to hemodilution, hypotension, hypothermia, isolation of the lungs from the circulation, and possible sequestration of drug in the bypass circuit [33]. The asymmetrical distribution of propofol during CPB surgery due to cross-clamping [34] as well as the fact that sevoflurane could be superior to propofol with respect to blood flow in left ventricular assist devices [11].

Study limitations

The present study is subject to a series of limitations. First, the effects of inhaled anesthetics [8-10, 35] and the intravenous anesthesia (propofol, opioids) [36, 37] may be dose-dependent. The concentration of sevoflurane used represents approximately 1 minimum alveolar concentration, which is similar to the concentration used in other studies that show beneficial effects in a model of ischemia-reperfusion after thoracic-aortic occlusion in pigs [14]. A human study also reported beneficial effects of this concentration [38]. However, it cannot be excluded that different concentrations of these agents could produce different effects. Second, our investigation is performed 30 minutes after removal of partial aortic cross-clamping. Further investigations are necessary to evaluate long-term sevoflurane and propofol effects on reperfusion.

Conclusions

Sevoflurane and propofol are similar with respect to blood flow (in the brain, heart, lung, liver, kidney, and ileum), markers of cellular injury, inflammation, and nitric oxide in the reperfusion after partial thoracic aortic cross-clamping. These findings may have significant clinical implications for anesthesiologists regarding the possibility of using either sevoflurane or propofol in surgeries that need a partial aortic cross-clamping.

Acknowledgements

This study was supported by a grant from the Spanish Health Ministry (Fondo de Investigaciones Sanitarias) under contract FISPI08/1480. The authors gratefully acknowledge the cardiac surgeons for their help in running the Ventricular Assist Devices Program. The Gregorio Marañón University Hospital Ethics Committee for Animal Research approved the use of animals and all procedures described in this study.

Disclosure of conflict of interest

None.

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